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[List of Attached Documents]

[Document Name] Specification 1

[Document Name] Abstract 1

[Number of General Power of Attorney] 9705256

[Necessity of Proof] Needed

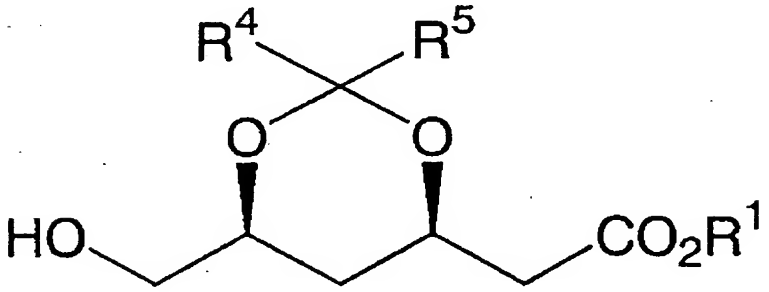
[Document Name] Specification

[Title of the Invention] Processes for the preparation of optically active 2-[6-(hydroxymethyl)-1,3-dioxane-4-yl] acetic acid derivatives

[Scope of Claims for Patent]

[Claim 1] A process for producing a following compound(I):

[Chemical 1]

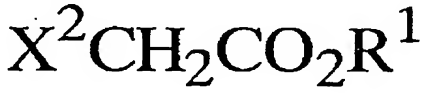


(I)

in the formula, R^1 represents any of hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^4 and R^5 independently represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^4 and R^5 may be joined to each other to form a ring,

which comprises (1) reacting an enolate prepared by permitting any of a base and a zerovalent metal to act upon an acetic acid ester derivative of the following formula (II):

[Chemical 2]

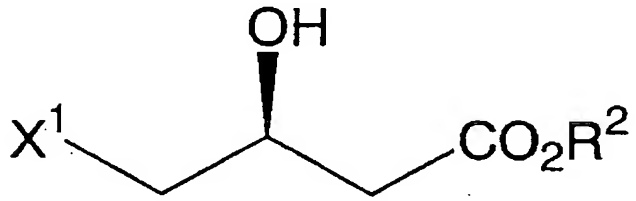


(II)

in the formula, R^1 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^2 represents a hydrogen or a halogen atom,

with a compound of the following formula (III):

[Chemical 3]

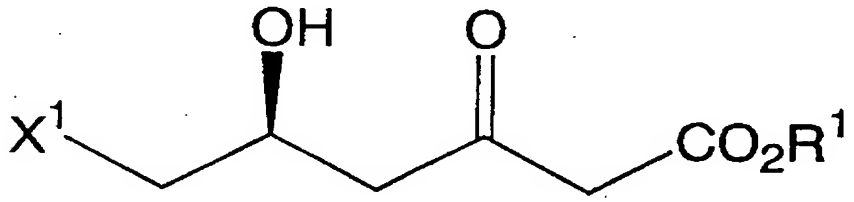


(III)

in the formula, R^2 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^1 represents a halogen atom,

at a temperature not below -30℃ to produce a compound of the following formula (IV):

[Chemical 4]

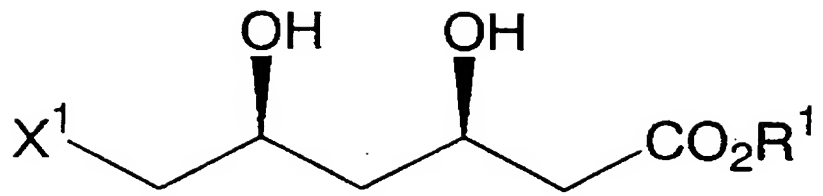


(IV)

in the formula, R^1 and X^1 are as defined above,

(2) further reducing this compound with using a microorganism to produce a compound of the following formula (V):

[Chemical 5]

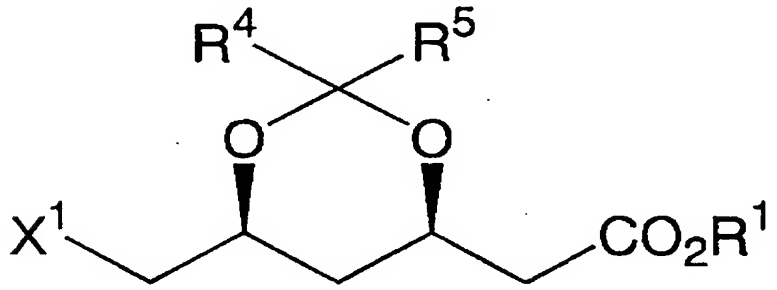


(V)

in the formula, R^1 and X^1 are as defined above,

(3) further treating this compound with an acetal forming reaction agent in the presence of an acid catalyst to produce a compound of the following formula (VI):

[Chemical 6]

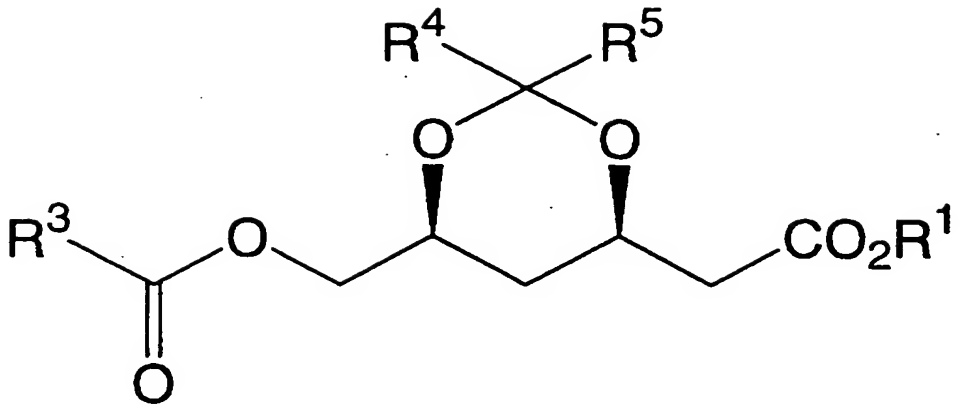


(VI)

in the formula, R^1 and X^1 are as defined above; R^4 and R^5 independently represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^4 and R^5 may be joined to each other to form a ring,

(4) further subjecting this compound for acyloxylation with an acyloxylation agent to produce a compound of the following formula (VII):

[Chemical 7]



(VII)

in the formula, R^1, R^4 and R^5 are as defined above and R^3 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms,

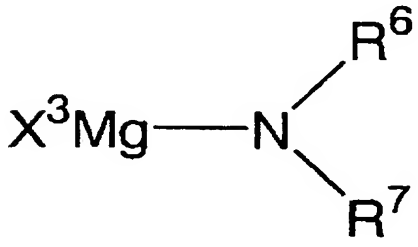
and (5) further subjecting this compound for solvolysis in the presence of a base.

[Claim 2] The process according to Claim 1,

wherein, referring to the acetic acid ester derivative, X^2 is a hydrogen atom

and a magnesium amide of the following formula (VIII):

[Chemical 8]



(VIII)

in the formula, R^6 and R^7 each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms,

an aralkyl group of 7 to 12 carbon atoms and a silyl group and X^3 represents a halogen atom,

is used as the base for enolate preparation.

[Claim 3] The process according to Claim 2,

wherein, referring to the magnesium amide, R^6 and R^7 each is an isopropyl group.

[Claim 4] The process according to any of Claims 2 and 3,

wherein, referring to the magnesium amide, X^3 is a chlorine atom.

[Claim 5] The process according to Claim 1,

wherein, referring to the acetic acid ester derivative, X^2 is a halogen atom

and any of a magnesium and a zinc is used as a zerovalent metal for enolate preparation.

[Claim 6] The process according to any of Claims 1 to 5,

wherein a polyether is added in the step of the reaction with the enolate.

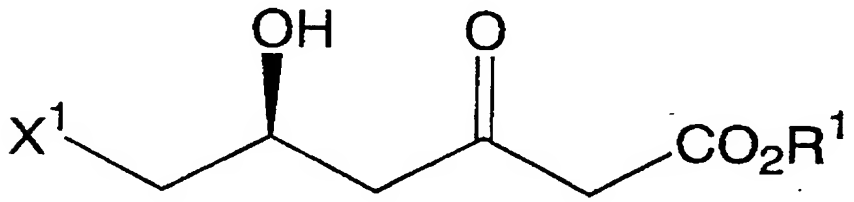
[Claim 7] The process according to Claim 6,

wherein dimethoxyethane is used as the polyether.

[Claim 8] The process according to Claim 1,

wherein a compound of the following formula (IV):

[Chemical 9]

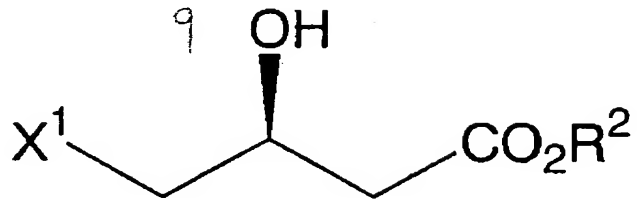


(IV)

in the formula, R^1 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^1 represents a halogen atom,

is produced by treating the compound of the following formula (III):

[Chemical 10]



(III)

in the formula, R^2 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^1 is as defined above,

with a Grignard reagent of the following formula (IX) in advance:

[Chemical 11]

(IX)

in the formula, R^8 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^4 represents a halogen atom,

and reacting with an enolate prepared by permitting any of a base and a zerovalent metal to act upon an acetic acid ester derivative of the following formula (II):

[Chemical 12]

$$X^2CH_2CO_2R^1$$

(I I)

in the formula, R^1 is as defined above and X^2 represents a hydrogen or a halogen atom,

at a temperature not below -30℃.

[Claim 9] The process according to Claim 8,

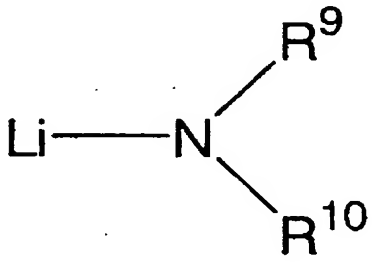
wherein, referring to the Grignard reagent, R^8 represents a tert-butyl group and X^4 represents a chlorine atom.

[Claim 10] The process according to any of Claims 8 or 9,

wherein, referring to the acetic acid ester derivative, X^2 is a hydrogen atom

and a lithium amide of the following formula (X):

[Chemical 13]



(X)

in the formula, R^9 and R^{10} each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

is used as a base for enolate preparation.

[Claim 11] The process according to any of Claims 8 to 10,

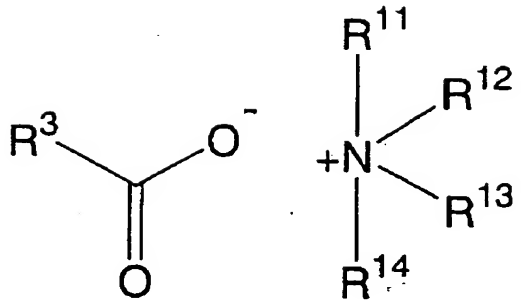
wherein, referring to the lithium amide, R^9 and R^{10} each is an isopropyl group.

[Claim 12] The process according to any of Claims 1 to 11, wherein, referring to the step of reduction using the microorganism, a culture, a cell or a treatment product of the microorganism selected from microorganisms belonging to the genera Hormoascus, Candida, Cryptococcus, Debaryomyces, Geotrichum, Kuraishia, Hansenula, Kluyveromyces, Pichia, Yamadazyma, Rhodotorula, Saccharomyces, Schizoblastsporion and Zygosaccharomyces.

[Claim 13] The process according to any of Claims 1 to 12, wherein, referring to the step of reduction using the microorganism, the microorganism to be used is selected from the group consisting of Hormoascus platypodis, Candida catenulatea, Candida diversa, Candida fructus, Candida glaebosa, Candida guilliermondii, Cryptococcus humicola, Candida intermedia, Candida magnoliae, Candida musae, Candida pintolopesii var. pintolopesii, Candida pinus, Candida sake, Candida sonorensis, Candida tropicalis, Cryptococcus laurentii, Cryptococcus terreus, Debaryomyces hansenii var. fabryi, Geotrichum eriense, Kuraishia capsulata, Kluyveromyces marxianus, Pichia bovis, Yamadazyma haplophilia, Pichia membranaefaciens, Rhodotorula glutinis, Saccharomyces cerevisiae, Shizoblastsporion kobayasii, Candida claussenii, Debaryomyces robertsii, Zygosaccharomyces rouxii.

[Claim 14] The process according to any of claims 1 to 13, wherein a quaternary ammonium carboxylate of the following formula (XI):

[Chemical 14]



(XI)

in the formula, R^3 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and R^{11}, R^{12}, R^{13} and R^{14} independently represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms,

is used as the acyloxylation agent.

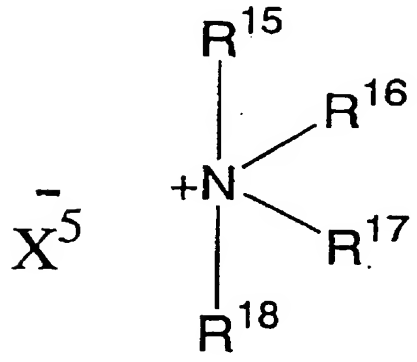
[Claim 15] The process according to Claim 14,

wherein, referring to the quaternary ammonium carboxylate, R^{11}, R^{12} R^{13} and R^{14} each is a n-butyl group.

[Claim 16] The process according to any of Claims 1 to 13,

wherein a mixture of a quaternary ammonium salt of the following formula (XII):

[Chemical 15]

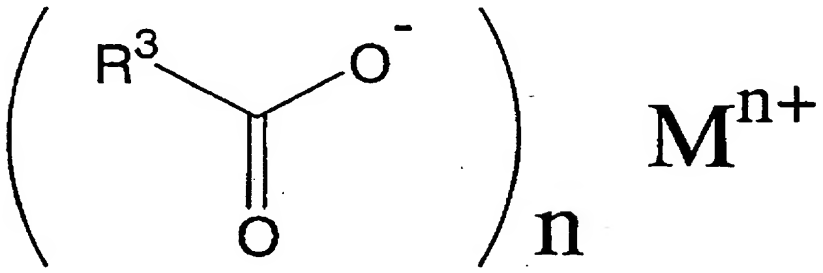


(XII)

in the formula, R^{15}, R^{16}, R^{17} and R^{18} independently represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^5 represents any of a halogen atom, a hydroxy group and an acyloxy group,

and a carboxylate of the following formula (XIII):

[Chemical 16]



(XIII)

in the formula, R^3 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; M represents any of an alkali metal and an alkaline earth metal; and n represents an integer of 1 or 2,

is used as the acyloxylation agent.

[Claim 17] The process according to Claim 16,

wherein, referring to the quaternary ammonium salt, R^{15}, R^{16}, R^{17} and R^{18} each is an n-butyl group.

[Claim 18] The process according to any of Claims 16 and 17,

wherein, referring to the quaternary ammonium salt, X^5 is any of a chlorine and a bromine.

[Claim 19] The process according to any of Claims 16 to 18,

wherein, referring to the carboxylate, M is any of a sodium and a potassium.

[Claim 20] The process according to any of Claims 16 to 19,

wherein the quaternary ammonium salt is used not more than the stoichiometric amount as a catalyst.

[Claim 21] The process according to any of Claims 1 to 20, wherein N,N-dimethylformamide is used as a solvent for acyloxylation reaction.

[Claim 22] The process according to any of Claims 1 to 21, wherein R^1 is a tert-butyl group.

[Claim 23] The process according to any of Claims 1 to 22, wherein R^2 is an ethyl group.

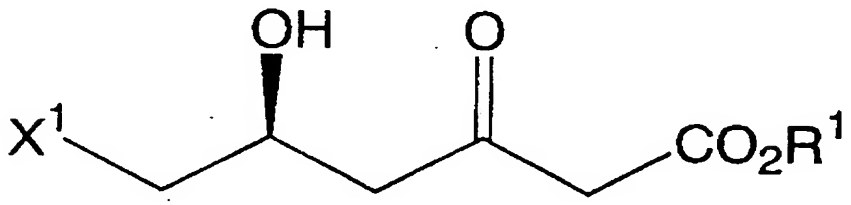
[Claim 24] The process according to any of Claims 1 to 23, wherein R^3 is a methyl group.

[Claim 25] The process according to any of Claims 1 to 24, wherein R^4 and R^5 each is a methyl group.

[Claim 26] The process according to any of Claims 1 to 25, wherein X^1 is a chlorine.

[Claim 27] A process of producing a compound of the following formula (IV):

[Chemical 17]

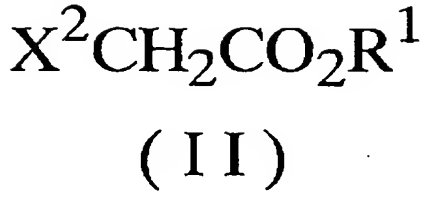


(IV)

in the formula, R^1 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^1 represents a halogen atom,

which comprises reacting an enolate prepared by permitting any of a base or a zerovalent metal to act upon an acetic acid ester derivative of the following formula (II):

[Chemical 18]

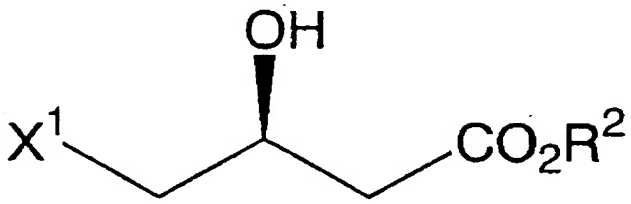


(II)

in the formula, R^1 is as defined above and X^2 represents a hydrogen or a halogen atom,

with a compound of the following formula (III):

[Chemical 19]



(III)

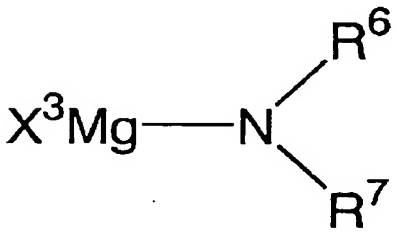
in the formula, R^2 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^1 is as defined above,

at a temperature not below -30℃.

[Claim 28] The process according to Claim 27,

wherein, referring to the acetic acid ester derivative, X^2 is a hydrogen atom

and a magnesium amide of the following formula (VIII):



(VIII)

in the formula, R^6 and R^7 each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group and X^3 represents a halogen atom,

is used as the base for enolate preparation.

[Claim 29] The process according to Claim 28,

wherein, referring to the magnesium amide, R^6 and R^7 each is an isopropyl group.

[Claim 30] The process according to any of Claims 28 and 29,

wherein referring to the magnesium amide, X^3 is a chlorine atom.

[Claim 31] The process according to Claim 27,

wherein, referring to the acetic acid ester derivative, X^2 is a halogen atom

and any of a magnesium and a zinc is used as a zerovalent metal for enolate preparation.

[Claim 32] The process according to any of Claims 27 to 31,

wherein a polyether is added in the step of the reaction with the enolate.

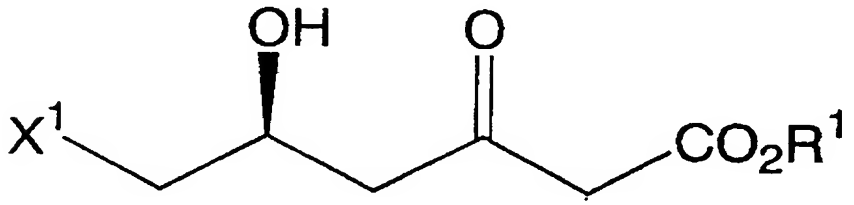
[Claim 33] The process according to Claim 32,

wherein dimethoxyethane is used as the polyether.

[Claim 34] The process according to Claim 27,

wherein a compound of the following formula (IV):

[Chemical 21]



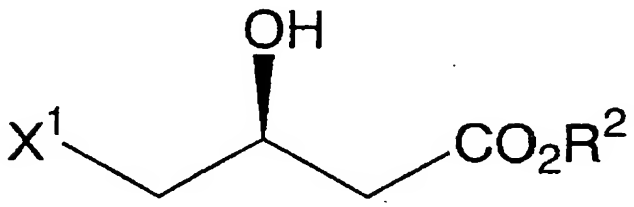
(IV)

in the formula, R^1 represents any of a hydrogen, an alkyl group

of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^1 represents a halogen atom,

is produced by treating the compound of the following formula (III):

[Chemical 22]



(III)

in the formula, R^2 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^1 is as defined above,

with a Grignard reagent of the following formula (IX) in advance:

[Chemical 23]

(IX)

in the formula, R^8 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^4 represents a halogen atom,

and reacting with an enolate prepared by permitting any of a base and a zerovalent metal to act upon an acetic acid ester derivative of the following formula (II):

[Chemical 24]

$$X^2CH_2CO_2R^1$$

(II)

in the formula, R^1 is as defined above and X^2 represents a hydrogen or a halogen atom,

at a temperature not below -30℃.

[Claim 35] The process according to Claim 34,

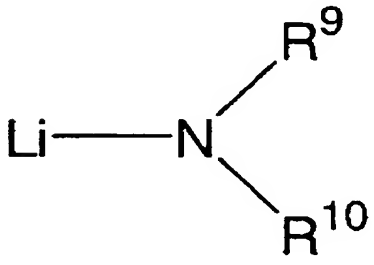
wherein, referring to the Grignard reagent, R^8 is a tert-butyl group and X^4 is a chlorine atom.

[Claim 36] The process according to any of Claims 34 and 35,

wherein, referring to the acetic acid ester derivative, X^2 is a hydrogen atom

and a lithium amide of the following formula (X):

[Chemical 25]



(X)

in the formula, R^9 and R^{10} each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and a silyl group,

is used as a base for enolate preparation.

[Claim 37] The process according to any of Claims 34 to 36,

wherein, referring to the lithium amide, R^9 and R^{10} each is an isopropyl group.

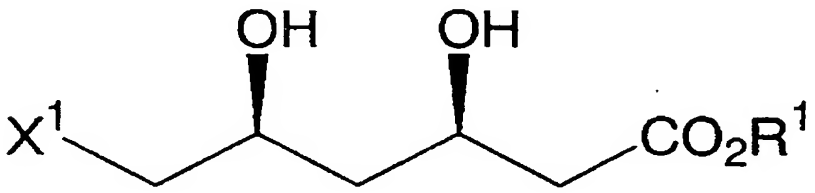
[Claim 38] The process according to any of Claims 27 to 37, wherein R^1 is a tert-butyl group.

[Claim 39] The process according to any of Claims 27 to 38, wherein R^2 is an ethyl group.

[Claim 40] The process according to any of Claims 27 to 39, wherein X^1 is a chlorine.

[Claim 41] A process for producing a compound of the following formula (V):

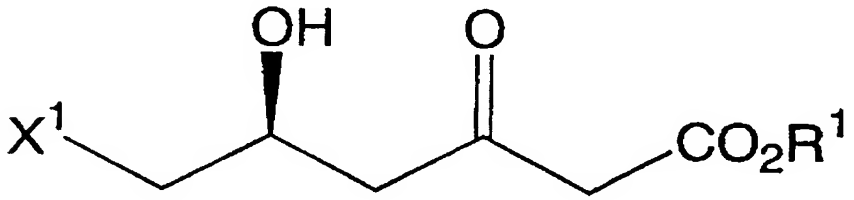
[Chemical 26]



(V)

in the formula, R^1 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^1 represents a halogen atom,

which comprises reducing a compound of the following formula (IV):



(IV)

in the formula, R^1 and X^1 are as defined above,

with using a microorganism.

[Claim 42] The process according to Claim 41,

wherein, referring to the step of reduction using the microorganism, a culture, a cell or a treatment product of the microorganism selected from microorganisms belonging to the genera Hormoascus, Candida, Cryptococcus, Debaryomyces, Geotrichum, Kuraishia, Hansenula, Kluyveromyces, Pichia, Yamadazyma, Rhodotorula, Saccharomyces, Schizoblastsporion and Zygosaccharomyces.

[Claim 43] The process according to any of Claims 41 and 42,

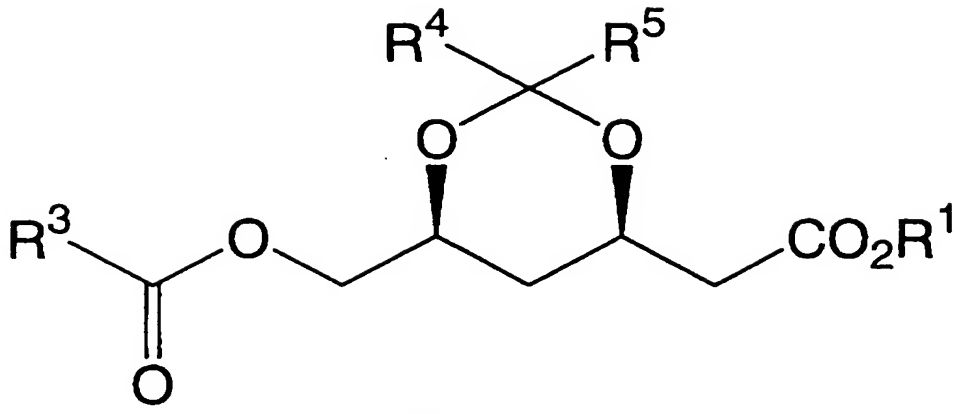
wherein, referring to the step of reduction using the microorganism, the microorganism to be used is selected from the group consisting of Hormoascus platypodis, Candida catenulatea, Candida diversa, Candida fructus, Candida glaebosa, Candida guilliermondii, Cryptococcus humicola, Candida intermedia, Candida magnoliae, Candida musae, Candida pintolopesii var. pintolopesii, Candida pinus, Candida sake, Candida sonorensis, Candida tropicalis, Cryptococcus laurentii, Cryptococcus terreus, Debaryomyces hansenii var. fabryi, Geotrichum eriense, Kuraishia capsulata, Kluyveromyces marxianus, Pichia bovis, Yamadazyma haplophilia, Pichia membranaefaciens, Rhodotorula glutinis, Saccharomyces cerevisiae, Shizoblastsporion kobayasii, Candida claussenii, Debaryomyces robertsii, Zygosaccharomyces rouxii.

[Claim 44] The process according to any of Claims 41 to 43, wherein R^1 is a tert-butyl group.

[Claim 45] The process according to any of Claims 41 to 44, wherein X^1 is a chlorine.

[Claim 46] A process for producing a compound of the following formula (VII):

[Chemical 28]

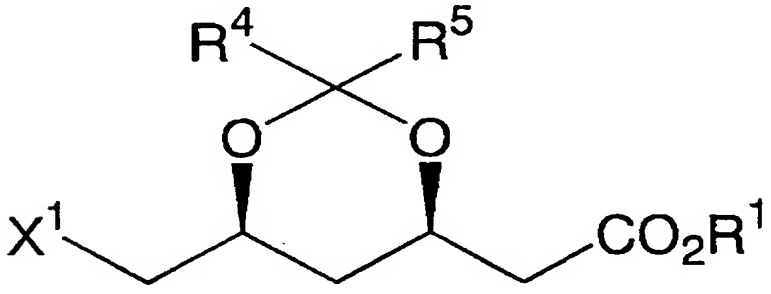


(VII)

in the formula, R^1 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^4 and R^5 independently represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^4 and R^5 may be joined to each other to form a ring; and R^3 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms,

which comprises subjecting a compound of the following formula (VI):

[Chemical 29]



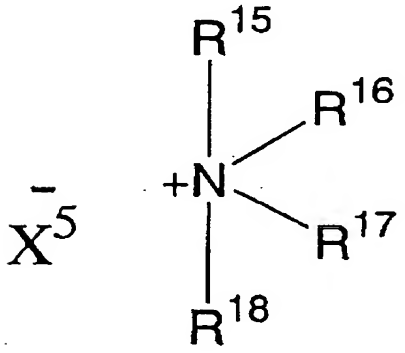
(VI)

in the formula, R^1 is as defined above, X^1 represents a halogen

atom and R^4 and R^5 are as defined above,

for acyloxylation with a mixture of a quaternary ammonium salt of the following formula (XII):

[Chemical 30]

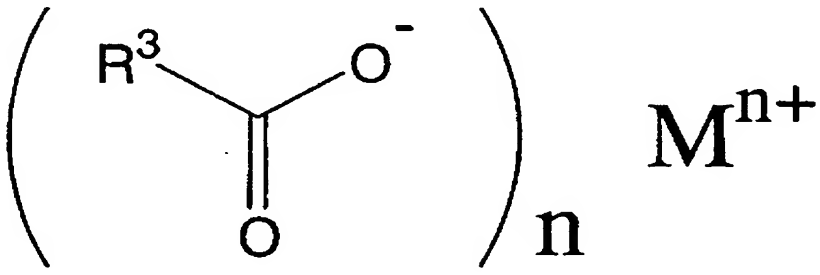


(XII)

in the formula, R^{15}, R^{16}, R^{17} and R^{18} independently represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^5 represents any of a halogen atom, a hydroxy group and an acyloxy group,

and a carboxylate of the following formula (XIII):

[Chemical 31]



(XIII)

in the formula, R^3 is as defined above, M represents any of an

alkali metal and an alkaline earth metal and n represents an integer of 1 or 2,

as an acyloxylation agent.

[Claim 47] The process according to Claim 46,

wherein, referring to the quaternary ammonium salt, R^{15}, R^{16}, R^{17} and R^{18} each is a n-butyl group.

[Claim 48] The process according to any of Claims 46 and 47,

wherein, referring to the quaternary ammonium salt, X^5 is any of a chlorine and a bromine.

[Claim 49] The process according to any of Claims 46 to 48,

wherein, referring to the carboxylate, M is any of a sodium and a potassium.

[Claim 50] The process according to any of Claims 46 to 49,

wherein the quaternary ammonium salt is used not more than the stoichiometric amount as a catalyst.

[Claim 51] The process according to any of Claims 46 to 50,

wherein N,N-dimethylformamide is used as a solvent for acyloxylation reaction.

[Claim 52] The process according to any of Claims 46 to 51,

wherein R^1 is a tert-butyl group.

[Claim 53] The process according to any of Claims 46 to 52,

wherein R^3 is a methyl group.

[Claim 54] The process according to any of Claims 46 to 53,

wherein R^4 and R^5 each is a methyl group.

[Claim 55] The process according to any of Claims 46 to 54,

wherein X^1 is a chlorine.

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention]

The present invention relates to a process for producing an optically active 2-[6-(hydroxymethyl)-1,3-dioxane-4-yl] acetic acid derivative which is of value as a pharmaceutical intermediate, particularly an intermediate of an HMG-CoA reductase inhibitor.

[0002]

[Prior Art]

The hitherto-known process for producing an optically active 2-[6-(hydroxymethyl)-1,3-dioxane-4-yl] acetic acid derivative includes the following processes.

(1) The process of synthesizing a 3,5,6-trihydroxyhexanoate ester derivative via a 3,5-dihydroxyhexanoate ester derivative using a 3-hydroxy-γ-butyrolactone as a starting material (Japanese Kokai Publication Hei-4-173767).

(2) The process of synthesizing a 3,5,6-trihydroxyhexanoate ester derivative via a 3,5-dihydroxyhexanoate ester derivative using a 3,4-dihydroxybutylnitrile acetonide as a starting material (Japanese Kokai Publication Hei-2-262537).

(3) The process in which a 4-chloro-acetoacetic acid ester is benzyloxylated, followed by reduction and carburization to be transformed to a 3,5,6-trihydroxyhexanoate ester derivative (Japanese Kokai Publication Hei-6-65226).

(4) The process of synthesizing a 3,5,6-trihydroxyhexanoate ester derivative via steps such as carbulization, reduction and the like using a 4-chloro-3-hydroxybutyric acid ester as a starting material (US 5278313).

(5) The process of synthesizing a 3,5,6-trihydroxyhexanoate ester derivative via a 2,4-dihydroxyadipic acid derivative using a malic acid as a starting material (Japanese Kokai Publication Hei-4-69355).

[0003]

However, these processes involves a very low temperature reaction around -80℃ (1, 2, 4, and 5) and a high pressure hydrogenation reaction at 100 kg/cm^2 (3) as a part of the production process and require the extraordinary reaction equipment. Further, these require expensive starting materials in many steps so that these are not favorable processes for commercial-scale production.

[0004]

In the prior art (4), for example, first step comprises reacting a tert-butyl acetic acid enolate with a

4-chloro-3-hydroxybutyric acid ester under a very low temperature of -78℃ using an expensive lithium hexamethyldisilazide as a base and the second step comprises a stereoselective reduction using an expensive diethylmethoxyborane and a sodium borohydride at a very low temperature of -78℃, again. Further, the forth step comprises an acetoxylation reaction by an expensive tetra-n-butyl ammonium acetate using an expensive 1-methyl-2-pyrrolidinone as a solvent.

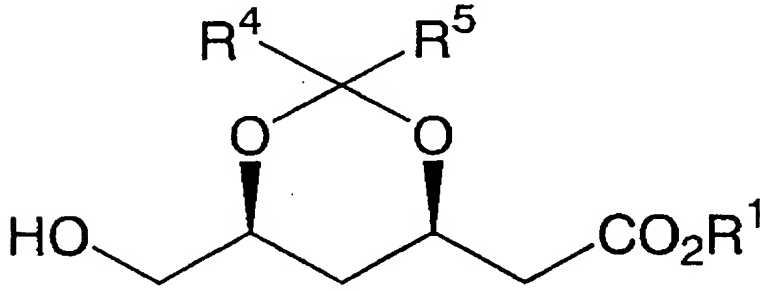
[0005]

[Subject which the Invention is to solve]

The object of the present invention, in the above perspective, is to provide a production process by which an optically active 2-[6-(hydroxymethyl)-1,3-dioxane-4-yl] acetic acid derivative of the following formula (I), a useful pharmaceutical intermediate, can be prepared easily from a readily available, inexpensive starting material without using any extraordinary production equipment such as a very-low-temperature reactor:

[0006]

[Chemical 32]



(I)

[0007]

in the formula, R^1 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms

and an aralkyl group of 7 to 12 carbon atoms; R^4 and R^5 independently represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^4 and R^5 may be joined to each other to form a ring.

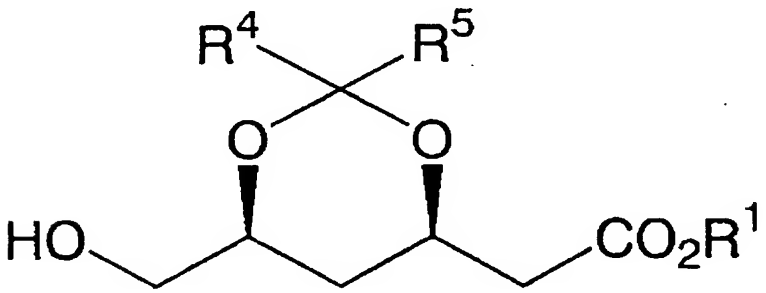
[0008]

[Means for solving the problem]

The inventors of the present invention made intensive investigations in view of the above state of the art and found that, starting with a readily available, inexpensive starting material, an optically active 2-[6-(hydroxymethyl)-1,3-dioxane-4-yl] acetic acid derivative of the following formula (I) can be produced without using any extraordinary production equipment such as a very-low-temperature reactor:

[0009]

[Chemical 33]



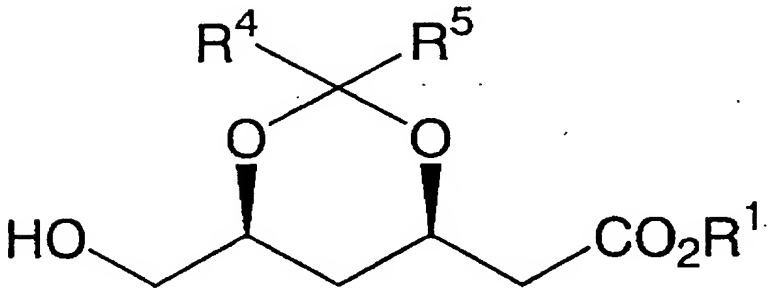
(I)

[0010]

in the formula, R^1 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^4 and R^5 independently represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^4 and R^5 may be joined to each other to form a ring.

[0011]
The present invention, therefore, relates to a process for producing an optically active 2-[6-(hydroxymethyl)-1,3-dioxane-4-yl] acetic acid derivative of the following formula (I):

[0012]
[Chemical 34]

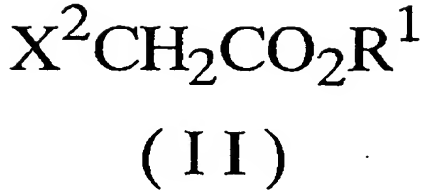


(I)

[0013]
in the formula, R^1 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; R^4 and R^5 independently represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms; and R^4 and R^5 may be joined to each other to form a ring,

which comprises (1) the step reacting an enolate prepared by permitting any of a base and a zerovalent metal to act upon an acetic acid ester derivative of the following formula (II):

[0014]
[Chemical 35]

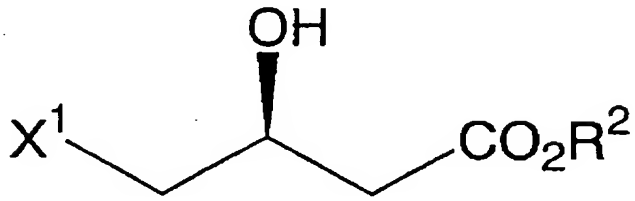


(II)

[0015]
in the formula, R^1 is as defined above and X^2 represents a hydrogen or a halogen atom,

with a compound of the following formula (III):

[0016]
[Chemical 36]

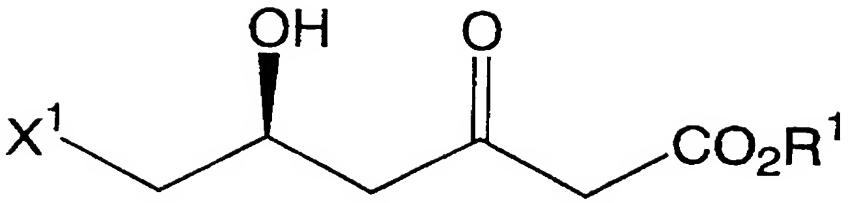


(III)

[0017]
in the formula, R^2 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and X^1 represents a halogen atom,

at a temperature not below −30 ℃ to prepare a compound of the following formula (IV):

[0018]
[Chemical 37]

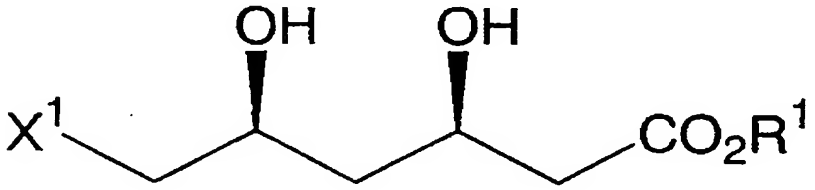


(IV)

[0019]
in the formula, R^1 and X^1 are as defined above,

(2) the step reducing this compound with using an microorganism to produce a compound of the following formula (V):

[0020]
[Chemical 38]

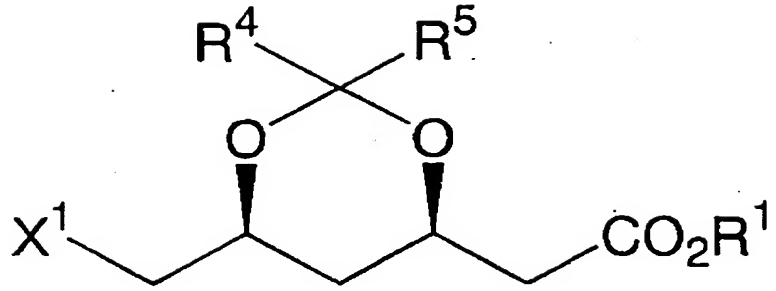


(V)

[0021]
in the formula, R^1 and X^1 are as defined above,

(3) the step treating this compound with an acetal forming reaction agent in the presence of an acid catalyst to produce a compound of the following formula (VI):

[0022]
[Chemical 39]



(VI)

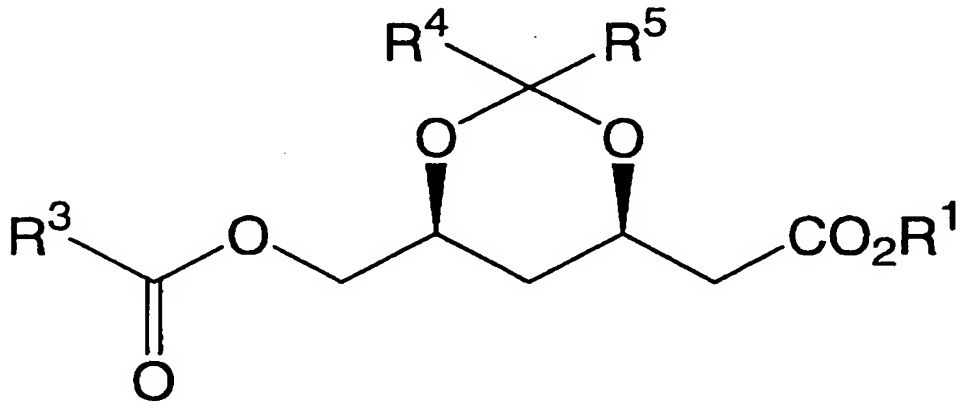
[0023]

in the formula, R^1, X^1, R^4 and R^5 are as defined above,

(4) the step subjecting this compound for acyloxylation with an acyloxylation agent to produce a compound of the following formula (VII):

[0024]

[Chemical 40]



(VII)

[0025]

in the formula, R^1, R^4 and R^5 are as defined above and R^3 represents any of a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms,

and (5) the step subjecting this compound for solvolysis in the presence of a base.

The present invention is now described in detail.

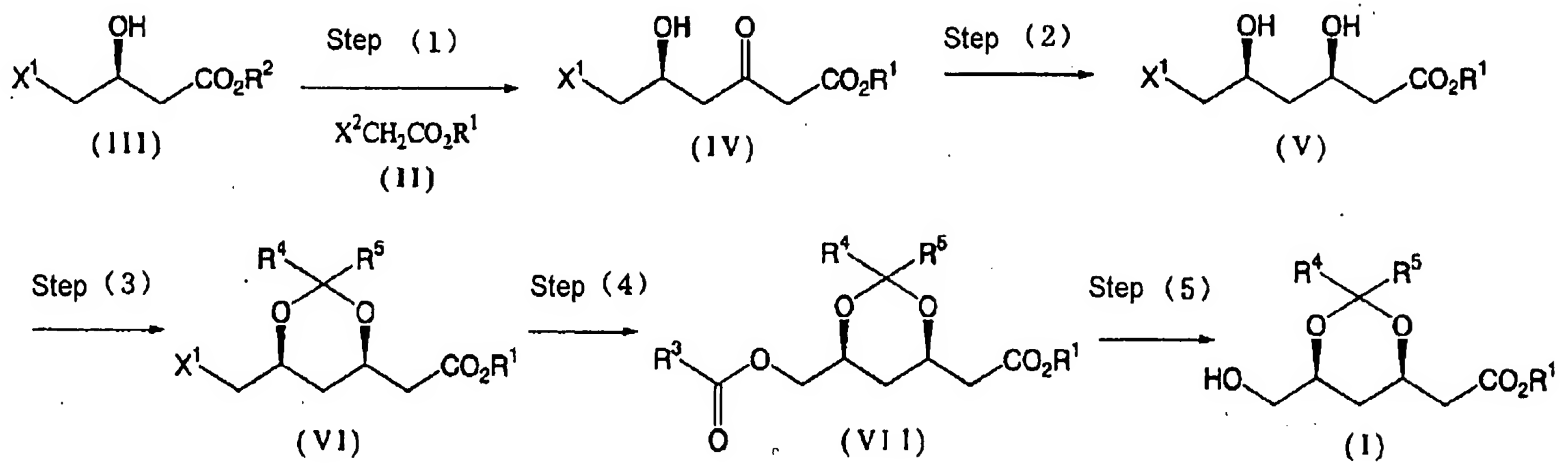
[0026]

[Modes for carrying out the Invention]

The present invention consist of five steps of non-very-low temperature reactions as indicated in the following reaction formula:

[0027]

[Chemical 41]


OH
X1
CO2R2
(III)
Step (1)
X2CH2CO2R1
(II)
OH
O
X1
CO2R1
(IV)
Step (2)
OH
OH
X1
CO2R1
(V)
Step (3)
R4
R5
O
O
X1
CO2R1
(VI)
Step (4)
R4
R5
O
O
R3
O
O
CO2R1
(VII)
Step (5)
R4
R5
O
O
HO
CO2R1
(I)

[0028]

In the following, the present invention is described in detail by following each step.

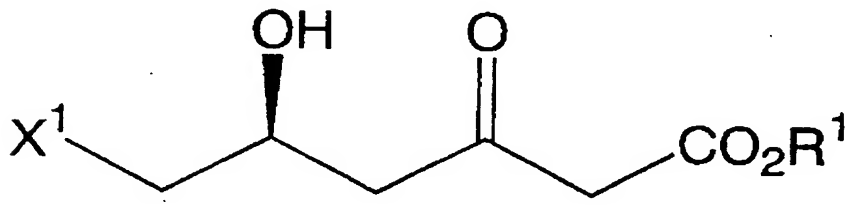
[0029]

Step (1)

In this step, a hydroxyoxohexanoate derivative having the (5S) configuration of the following formula (IV):

[0030]

[Chemical 42]



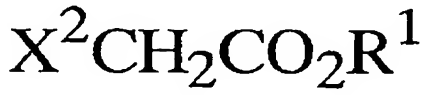
(IV)

[0031]

is produced by reacting an enolate prepared by permitting any of a base and a zerovalent metal to act upon an acetic acid ester derivative of the following formula (II):

[0032]

[Chemical 43]



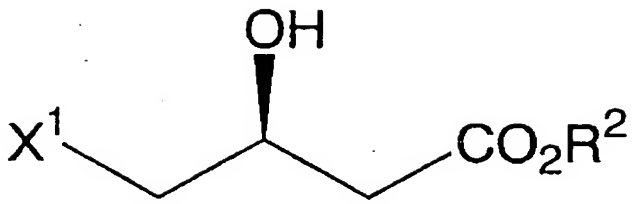
(II)

[0033]

with a hydroxybutyric acid derivative having the (3S) configuration of the following formula (III):

[0034]

[Chemical 44]



(III)

[0035]

at a temperature not below -30 ℃.

[0036]

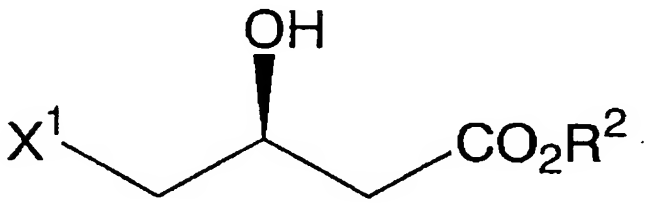
When a reaction involving an enolate such as an acetate-derived enolate is conducted at a non-very-low reaction temperature, for example not below -30 ℃, the self-condensation of the enolate proceeds predominantly to remarkably sacrifice the rate of conversion of the objective reaction. However, in the following process developed by the present inventors, the self-condensation of the acetic enolate can be minimized so that the objective reaction can be carried out in high yield.

[0037]

Referring to the hydroxybutyric acid derivatives to be used in the step (1), namely, the following compound (III):

[0038]

[Chemical 45]



(III)

[0039]

the configuration at position 3 is (S) form and R^2 is an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and the like. Specifically, there may be mentioned methyl, ethyl, isopropyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl and p-nitrobenzyl, among others and preferred are methyl and ethyl. More preferred is ethyl.

[0040]

Further, X^1 represents a halogen atom and specifically, there may be mentioned chlorine, bromine, iodine and the like. Preferred are chlorine and bromine and more preferred is chlorine. The optically active hydroxybutyric acid derivatives having the (3S) configuration can be produced in large amount in accordance with the known production processes (e.g. Patent Document No.1723728).

[0041]

Referring to the acetic acid ester derivatives to be used in the step (1), R^1 is a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and the like and specifically includes a hydrogen and methyl, ethyl, isopropyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl and p-nitrobenzyl among others. Preferred is tert-butyl.

[0042]

Further, X^2 represents a hydrogen or a halogen atom and there may be mentioned, specifically, halogen, chlorine, bromine, iodine, etc. Preferred are hydrogen, iodine and the like.

[0043]

The amount of use of the acetic acid ester derivative relative to the hydroxybutyric acid derivative is 1 to 10 molar equivalents, preferably 1 to 5 molar equivalents.

[0044]

In the step (1), the enolate is prepared by reacting the acetic acid ester derivative with any of a base or a zerovalent metal.

Generally, when X^2 of the acetic acid ester is a hydrogen, a base is used for enolate preparation and in the case X^2 is a halogen atom, a zerovalent metal is used for enolate preparation.

[0045]

As the base to be used for enolate preparation, there may be mentioned, for example, lithium amides such as lithium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethyldisilazide, etc.; magnesium amides such as magnesium diisopropylamide chloride, magnesium diisopropylamide bromide, magnesium diisopropylamide iodide, magnesium dicyclohexylamide chloride, etc.; sodium amides such as sodium amide, sodium diisopropylamide, etc.; potassium amides such as potassium amide, potassium diisopropylamide, etc.; alkyl lithium such as methyl lithium, n-butyl lithium, tert-butyl lithium, etc.; Grignard reagents such as methylmagnesium bromide, isopropylmagnesium chloride, tert-butylmagnesium chloride, etc.; metal alkoxides such as sodium methoxide, magnesium ethoxide, potassium tert-butoxide, etc.; metal hydrides such as lithium hydride, sodium hydride, potassium hydride, calcium hydride and the like.

[0046]

Preferred as a base are magnesium amides, lithium amides, Grignard reagents and the like.

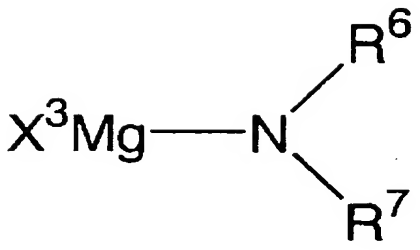
These bases are used singly or in a combination. For example, lithium amides are effective when combined with Grignard reagents.

[0047]

The magnesium amide is represented by the general formula (VIII):

[0048]

[Chemical 46]



(VIII)

[0049]

Here, R^6 and R^7 each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms, and a silyl group. Specifically, there may be mentioned methyl, ethyl, isopropyl, tert-butyl, cyclohexyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, p-nitrobenzyl, trimethylsilyl, triethylsilyl and phenyldimethylsilyl, among others. Preferred is isopropyl. X^3 represents a halogen atom and preferred are chlorine, bromine and iodine, among others. More preferred is chlorine.

[0050]

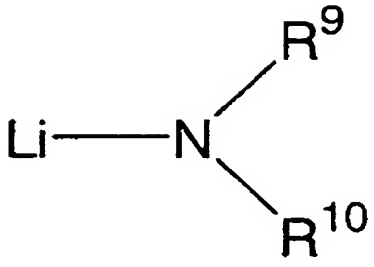
The magnesium amide can be prepared by a readily available, inexpensive secondary amine and a Grignard reagent in accordance with the known process (e.g. Japanese Kokai Publication Hei-8-523420). It also can be prepared by a lithium amide and a magnesium halide in accordance with the known process (e.g. J. Org. Chem. 1991, 56, pp.5978-5980).

[0051]

The lithium amide is represented by the general formula (X):

[0052]

[Chemical 47]



(X)

[0053]

Here, R^9 and R^{10} each represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms, and a silyl group. Specifically, there can be mentioned methyl, ethyl, isopropyl, tert-butyl, cyclohexyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, p-nitrobenzyl, trimethylsilyl, triethylsilyl and phenyldimethylsilyl, among others. Preferred is isopropyl.

[0054]

The Grignard reagent is represented by the following general formula (IX):

[0055]

[Chemical 48]

(IX)

[0056]

Here, R^8 represents any of an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms, an aralkyl group of 7 to 12 carbon atoms and the like. Specifically, there may be mentioned methyl, ethyl, n-propyl, isopropyl, n-butyl,

tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, and p-nitrobenzyl, among others. Preferred are methyl, ethyl, isopropyl, n-butyl, tert-butyl, etc. More preferred is tert-butyl. X^4 represents a halogen atom. Preferred are chlorine, bromine, iodine and the like. More preferred is chlorine.

[0057]

The amount of use of the base in the step (1) relative to the hydroxybutyric acid derivative is 1 to 10 molar equivalents, preferably 2 to 6 molar equivalents.

[0058]

The zerovalent metal which can be used for enolate preparation in the step (1) is zinc, magnesium, tin and the like. Preferred are zinc and magnesium.

The amount of use of the zerovalent metal in the step (1) relative to the hydroxybytyric acid derivative is 1 to 20 molar equivalents, preferably 2 to 8 molar equivalents.

[0059]

The solvent which can be used in the step (1) may for example be an aprotic organic solvent. The organic solvent mentioned above includes hydrocarbon solvents such as benzene, toluene, n-hexane, cyclohexane, etc.; ether solvents such as diethyl ether, tetrahydrofuran, 1,4-dioxane, methyl t-butyl ether, dimethoxymethane, ethylene glycol dimethyl ether, etc.; halogen-containing solvents such as methylene chloride, chloroform, 1,1,1-trichloroethane, etc.; and aprotic polar solvents such as dimethylformamide, N-methylpyrrolidone, hexamethylphosphoric triamide, etc., among others. These solvents may be used each alone or two or more of them may be used in a suitable combination. Preferred, among the above-mentioned solvents, are hydrocarbon solvents, such as benzene, toluene, n-hexane, cyclohexane, etc., and polyether solvents, such as diethyl ether, tetrahydrofuran, 1,4-dioxane, methyl t-butyl ether, dimethoxyethane, diethylene glycol dimethyl ether and so on. Polyether solvents may be used as the

sole solvent, but may be added 1 to 10 molar equivalents relative to the hydroxybutyric acid derivative in other reaction solvents as an additive. Among these, preferred is dimethoxyethane.

[0060]

The reaction temperature for the reaction in the step (1) is preferably -30 ℃ to 100 ℃, more preferably -10 ℃ to 60 ℃.

[0061]

In the step (1), the order of mixing of reaction agents is arbitrary, however, preferably, the reaction may be conducted by adding the base to a mixed solution containing the hydroxybutyric acid derivative and the acetic acid ester derivative.

[0062]

More preferably, the solution of Grignard reagents such as methylmagnesium bromide, isopropylmagnesium chloride, tert-butylmagnesium chloride, etc. or magnesium amides such as magnesium diisopropylamide chloride, magnesium diisopropylamide bromide, magnesium diisopropylamide iodide, magnesium dicyclohexylamide chloride is added dropwise to a mixed solution containing the hydroxybutyric acid derivative and the acetic acid ester derivative in advance, and, then, the reaction may be conducted by adding further the solution of lithium amides such as lithium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethydisilazide, etc. or magnesium amides dropwise.

Further, the reaction may be conducted by treating the hydroxybutyric acid derivative with the Grignard reagent in advance and reacting the same with the enolate prepared by permitting the zerovalent metal to act upon the acetic acid ester derivative.

[0063]

After completing the reaction of step (1), the routine aftertreatment may be carried out to recover the reaction product from a reaction mixture. A typical procedure may comprise blending the reaction mixture at completion of the reaction with

an aqueous solution of the common inorganic or organic acid, such as hydrochloric acid, sulfuric acid, nitric acid, acetic acid and citric acid, and carrying out an extraction with the common extractant such as ethyl acetate, diethyl ether, methylene chloride, toluene and hexane. From the obtained extract, the reaction solvent and extractant are distilled by heating under reduced pressure or the like procedures, whereby the objective product can be obtained. The objective product thus obtained is almost pure, however, it can be purified by the routine technique, such as crystallization, fractional distillation, column chromatography and/or the like to further enhance its purity.

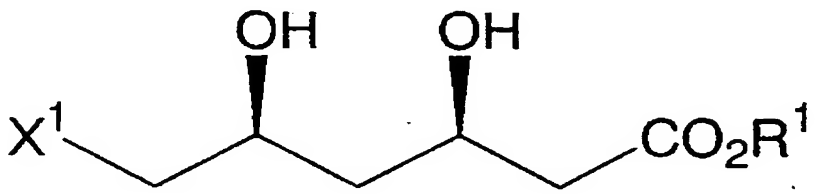
[0064]

Step (2)

In this step, a dihydroxyhexanoate derivative having the (3R, 5S) configuration of the following formula (V):

[0065]

[Chemical 49]



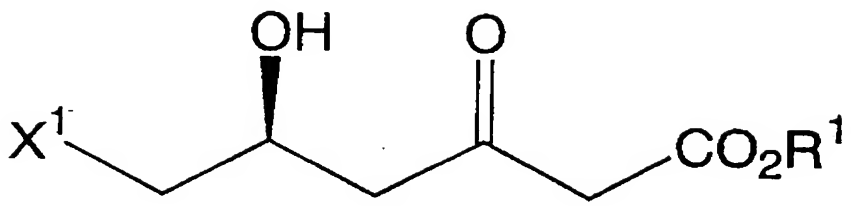
(V)

[0066]

is produced by reducing the hydroxyoxohexanoate derivative having the (5S) configuration of the following formula (IV) obtained in the step (1):

[0067]

[Chemical 50]



(IV)

[0068]

with using a microorganism.

[0069]

Generally, when reducing a carbonyl group of a hydroxyoxohexanoate derivative as shown in above in a highly stereoselective manner, the method comprising reducing by a hydrido reducing agent such as sodium borohydride in the presence of an alkyl borane under a very low temperature condition (e.g. US 5278313) is conducted.

The inventors of the present invention found a reduction method using a microorganism in order to reduce a hydroxyoxohexanoate derivative in an inexpensive and stereoselective way at a non-very-low temperature.

[0070]

A microorganism, which to be used in the step (2) and which transform a hydroxyoxohexanoate derivative into a dihydroxyhexanoate derivative by reduction, can be found by the method described below. For example, a 500 ml-volume Sakaguchi flask is charged with 50ml of A medium (pH 6.5) composed of 5% glucose, 0.5% peptone, 0.2% potassium dihydrogen phosphate, 0.1% dipotassium hydrogen phosphate, 0.02% magnesium sulfate and 0.1% yeast extract followed by the sterilization. A microorganism is seeded and shake-cultured at 30℃ for 2 to 3 days. The cells are collected by centrifugation, suspended to 25 ml of phosphate buffer containing 0.1 to 0.5% of (5S)-6-chloro-5-hydroxy-3-oxohexanoate tert-butyl ester and 5% glucose and shaken at

30℃ for 2 to 3 days in the 500 ml-volume Sakaguchi flask. After transformation reaction, extraction is carried out by adding the same volume of ethyl acetate as the reaction solution. 6-Chloro-3,5-dihydroxyhexanoate tert-butyl ester produced is analyzed by high-performance liquid chromatography (column: Nacalai Tesque Cosmosil 5CN-R (4.6 mm x 250 mm), eluent: 1mM phosphoric acid aqueous solution/ acetonitrile=5/1, flow rate: 0.7 ml/min., detection: 210 nm, column temperature: 30℃, elution time ((3S, 5S)-6-chloro-3,5-dihydroxyhexanoate tert-butyl ester: 12.5 min., (3R, 5S)-6-chloro-3,5-dihydroxyhexanoate tert-butyl ester: 13.5 min., (5S)-6-chloro-5-hydroxy-3-oxohexanoate tert-butyl ester:17 min.).

[0071]

Usable as the microorganism in the present invention are microorganisms belonging to the genera Hormoascus, Candida, Cryptococcus, Debaryomyces, Geotrichum, Kuraishia, Hansenula, Kluyveromyces, Pichia, Yamadazyma, Rhodotorula, Saccharomyces, Schizoblastosporion, Zygosaccharomyces. Specifically, there can be used, for example, Hormoascus platypodis IFO1471, Candida catenulata IFO0745, Candida diversa IFO1019, Candida fructus IFO1581, Candida glaebosa IFO1353, Candida guilliermondii IFO0454, Cryptococcus humicola IFO0760, Candida intermedia IFO0761, Candida magnoliae IFO0705, Candida musae IFO1582, Candida pintolopesii var. pintolopesii IFO0729, Candida pinus IFO0741, Candida sake IFO0435, Candida sonorensis IFO10027, Candida tropicalis IFO1401, Cryptococcus Laurentii IFO0609, Cryptococcus terreus IFO0727, Debaryomyces hansenii var. fabryi IFO0058, Geotrichum eriense ATCC22311, Kuraishia capsulata IFO0721, Kluyveromyces marxianus IFO0288, Pichia bovis IFO1886, Yamadazyma haplophila IFO0947, Pichia membranaefaciens IFO0458, Rhodotorula glutinis IFO1099, Saccharomyces cerevisiae IFO0718, Shizoblastosporion kobayasii IFO1644, Candida claussenii IFO0759, Debaryomyces robertsii IFO1277, Zygosaccharomyces rouxii IFO0493, etc. These microorganisms are generally obtainable from available or purchasable stock cultures. They

may also be isolated from the natural world. It is also possible to mutate these microorganisms to obtain strains which have more advantageous characteristics for the reaction.

[0072]

Any nutrient sources assimilable by these organisms can generally be used in cultivating these organisms. For example, carbon sources such as carbohydrates, e.g. glucose, sucrose and maltose, organic acids, e.g. lactic acid, acetic acid, citric acid and propionic acid, alcohols, e.g. ethanol and glycerol, hydrocarbons, e.g. paraffin, fats and oils such as soybean oil and rapeseed oil, and mixtures of these, and nitrogen sources such as ammonium sulfate, ammonium phosphate, urea, yeast extract, meat extract, peptone and corn steep liquor may be admixed. Furthermore, other inorganic salts, vitamins and like nutrients may also be incorporated in appropriate amounts as necessary.

[0073]

The microorganisms can be cultivated under ordinary conditions in general use, for example aerobically at a pH of 4.0 to 9.5 in a temperature range of 20℃ to 45℃ for 10 to 96 hours. In cases where the hydroxyoxohexanoate derivative is reacted with such a microorganism, the culture fluid of the above microorganisms can generally be submitted to the reaction as it is. A concentrate of the culture fluid may also be used. If a component in the culture fluid produces an adverse effect on the reaction, cells obtained by treating the culture fluid by centrifugation, for instance, or a product obtained by treating the cells is preferably used.

[0074]

The above-mentioned product of treatment of microbial cells is not particularly restricted but mention may be made of, for example, dried cells obtained by dehydration using acetone or diphosphorus pentoxide or by drying utilizing a desiccator or fan, products of treatment with a surfactant, products of treatment with a bacteriolytic enzyme, immobilized cells or cell-free extract preparations obtained by disrupting

cells, among others. Furthermore, an enzyme catalyzing the asymmetric reduction as purified from the culture may also be used.

[0075]

In carrying out the reduction reaction, the substrate hydroxyoxohexanoate derivative may be added all at once in the beginning of the reaction or in divided portions as the reaction proceeds.

[0076]

The reaction temperature is generally 10 to 60℃, preferably 20 to 40℃, and the pH during the reaction is 2.5 to 9, preferably 5 to 9.

[0077]

The microorganism concentration in the reaction mixture may be selected appropriately depending on the ability thereof to reduce the substrate. The substrate concentration in the reaction mixture is preferably 0.01 to 50% (w/v), more preferably 0.1 to 30%.

[0078]

The reaction is generally carried out with shaking or aeration and stirring. The reaction time may be selected according to the substrate concentration, microorganism concentration and other reaction conditions. Generally, the conditions are preferably selected so that the reaction may be complete in 2 to 168 hours.

[0079]

For promoting the reduction reaction, such an energy source as glucose or ethanol is preferably added to the reaction mixture in an amount of 1 to 30%, whereby better results can be obtained. Further, by adding a coenzyme, such as reduced form nicotinamide adenine dinucleotide (NADH) or reduced form nicotinamide adenine dinucleotide phosphate (NADPH), which is generally required for reduction reactions using the biological method, it is also possible to promote the reaction. Specifically, such may be added directly to the reaction mixture or a reaction system having

an ability of causing formation of NADH or NADPH may be added to the reaction mixture together with such a coenzyme in the oxide form. For example, the reaction system in which enzyme formate dehydrogenase reduces NAD to NADH on the occasion of its forming carbon dioxide and water from formic acid, or the reaction system in which glucose dehydrogenase reduces NAD or NADP to NADH or NADPH, respectively, on the occasion of its forming gluconolactone from glucose can be utilized.

It is also effective to add a surfactant, such as Triton (product of Nakalai Tesque), Span (product of Kanto Chemical) or Tween (product of Nakalai Tesque), to the reaction mixture. Further, for avoiding the inhibition of the reaction by an alcohol which is the substrate and/or the product of the reduction reaction, a water-insoluble organic solvent, such as ethyl acetate, butyl acetate, isopropyl ether or toluene, may be added to the reaction mixture. For increasing the solubility of the substrate, it is also possible to add a water-soluble organic solvent such as methanol, ethanol, acetone, tetrahydrofuran or dimethyl sulfoxide.

[0080]

The dihydroxyhexanoate derivative produced by the reduction reaction is obtainable by extracting the reaction mixture directly or after separation of cells, extracting with a solvent such as ethyl acetate or toluene and then removing the solvent. Further purification by recrystallization procedure or silica gel column chromatography, for instance, gives a highly pure form of the dihydroxyhexanoate derivative.

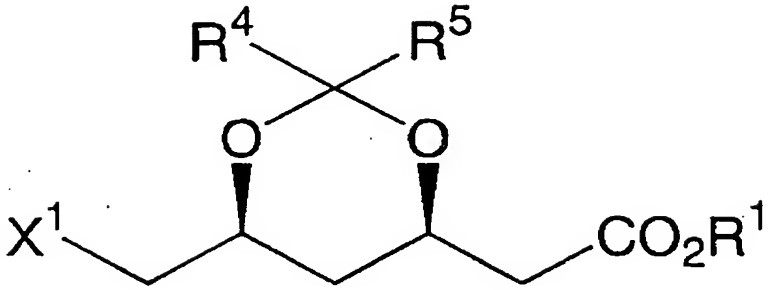
[0081]

Step (3)

In this step, a halomethyldioxanyl acetic acid derivative having the (4R, 6S) configuration of the following formula (VI):

[0082]

[Chemical 51]



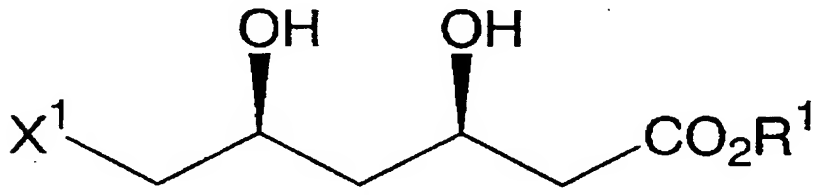
(VI)

[0083]

is produced subjecting the dihydroxyhexanoate derivative, having the (3R, 5S) configuration of the following formula (V) obtained in the step (2):

[0084]

[Chemical 52]



(V)

[0085]

to the known acetal forming reaction such as treating the same with an acetal forming reaction agent in the presence of an acid catalyst, for instance.

[0086]

In the step (3), usable as the acetal forming reaction agent are, for example, ketones, aldehydes, alkoxyalkanes, alkoxyalkenes, and the like. Specific examples for the above ketones, aldehydes, alkoxyalkanes and alkoxyalkenes are, for

example, acetone, cyclohexanone, formaldehyde, benzaldehyde, dimethoxymethane, 2,2-dimethoxypropane, 2-methoxypropene, 1,1-dimethoxycyclohexane, and the like. Preferred are acetone, 2-methoxypropene and 2,2-dimethoxypropane.

[0087]

The amount of use of the acetal forming reaction agent in the step (3) is preferably 1 to 10 molar equivalents, more preferably 1 to 5 molar equivalents relative to the dihydroxyhexanoate derivative. For the purpose of promoting the reaction, the acetal forming reaction agent can be used as an reaction solvent.

[0088]

Usable as the acid catalyst in the step (3) are Lewis acids and Bronsted acids. As the above Lewis acids and Bronsted acids, there can be mentioned, for example, Lewis acids such as aluminum trichloride, borate trifluoride, zinc dichloride, tin tetrachloride, etc.; carboxylic acids such as oxalic acid, formic acid, acetic acid, benzoic acid, trifluoroacetic acid, etc.; sulfonic acids such as methanesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, pyridinium p-toluenesulfonic acid, etc.; inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, boric acid, etc. Preferred are p-toluenesulfonic acid, camphorsulfonic acid and pyridinium p-toluenesulfonic acid.

[0089]

The amount of use of the acid catalyst in the step (3) is preferably 0.001 to 0.5 molar equivalent, more preferably 0.005 to 0.1 molar equivalent relative to the dihydroxyhexanoate derivative.

[0090]

The reaction of step (3) can be conducted without any solvent, but various organic solvents may be used as a reaction solvent. As the above organic solvents, there may be mentioned, for example, hydrocarbon solvents such as benzene, toluene, cyclohexane, etc.; ether solvents such as diethyl ether,

tetrahydrofuran, 1,4-dioxane, methyl t-butyl ether, dimethoxyethane, etc.; ester solvents such as ethyl acetate, butyl acetate, etc.; ketone solvents such as acetone, methyl ethyl ketone, etc.; halogen containing solvents such as methylene chloride, chloroform, 1,1,1-trichloroethane, etc.; nitrogen-containing solvents such as dimethylformamide, acetamide, formamide, acetonitrile, etc.; aprotic polar solvents such as dimethyl sulfoxide, N-methylpyrrolidone, hexamethylphosphoric triamide and so on. The above solvents may be used each alone or two or more of them may be used in a suitable combination. Preferred are toluene, acetone, methylene chloride, tetrahydrofuran, dimethylformamide, acetamide, formamide, acetonitrile, dimethyl sulfoxide, N-methylpyrrolidone, and so on.

[0091]

The reaction temperature of step (3) is -20 to 100℃, preferably 0 to 50℃.

[0092]

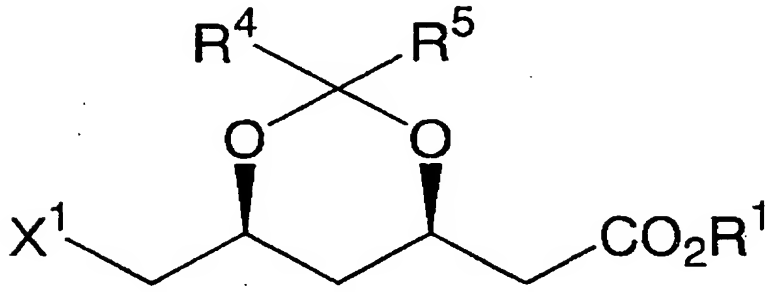
After completing the reaction of step (3), the routine aftertreatment may be carried out to recover the reaction product from a reaction mixture. For example, add water to the reaction mixture at completion of the reaction and carry out an extraction with the common extractant such as ethyl acetate, diethyl ether, methylene chloride, toluene and hexane. From the obtained extract, the reaction solvent and extractant are distilled by heating under reduced pressure or the like procedures, whereby the objective product can be obtained. Further, after completion of the reaction, the reaction solvent may be distilled immediately by heating under reduced pressure or the like procedures, followed by the same procedure. The objective product thus obtained is almost pure, however, it can be purified by the routine technique, such as crystallization, fractional distillation, column chromatography and/or the like to further enhance its purity.

[0093]

Referring to the halomethyldioxanyl acetic acid derivative, which is obtained in the step (3) of the following formula (VI):

[0094]

[Chemical 53]



(VI)

[0095]

R^4 and R^5 independently represents a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and the like, and specifically, there may be mentioned methyl, ethyl, tert-butyl, hexyl, phenyl, benzyl, p-methoxybenzyl and the like. Preferred is methyl.

[0096]

Further, R^4 and R^5 may be joined to each other to form a ring, for example, there may be mentioned the case that R^4 and R^5 form a ring to become a cyclopentane ring, cyclohexane ring, cycloheptane ring or benzocyclopentane ring resulting to form a spiro structure with 1,3-dioxane ring.

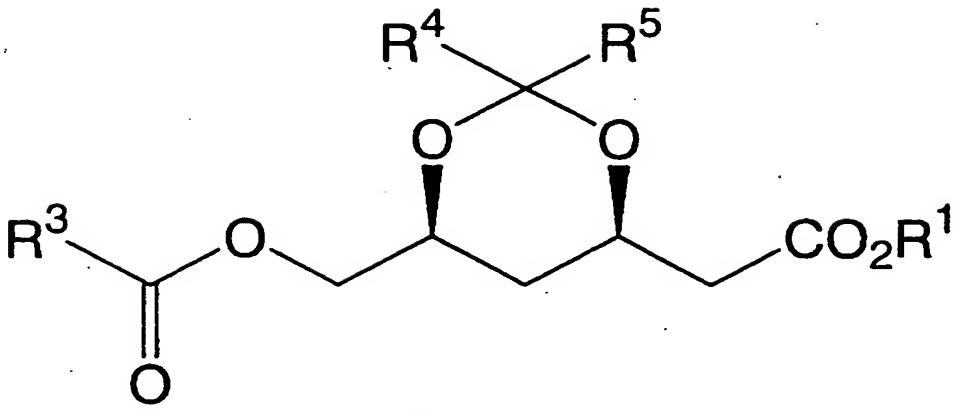
[0097]

Step (4)

In this step, an acyloxymethyldioxanyl acetic acid derivative having the(4R, 6S) configuration of the following formula (VII):

[0098]

[Chemical 54]



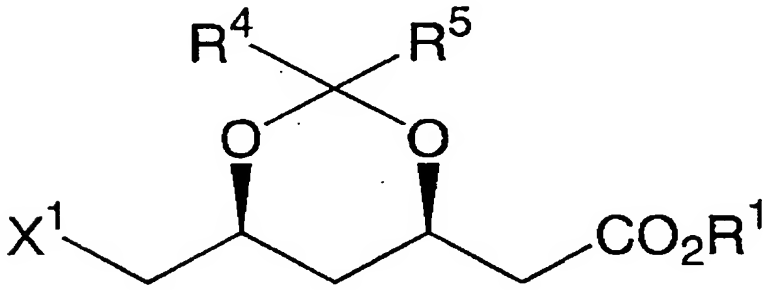
(VII)

[0099]

is produced by subjecting the halomethyldioxanyl acetic acid derivative having the (4R, 6S) configuration of the following formula (VI) obtained in the step (3):

[0100]

[Chemical 55]



(VI)

[0101]

for acyloxylation with an acyloxylation agent.

[0102]

Here, R^3 is a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group

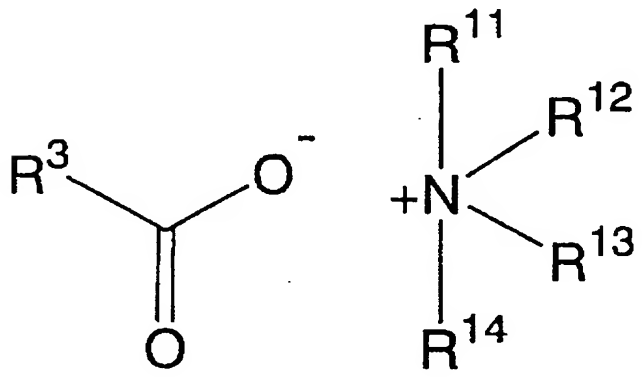
of 7 to 12 carbon atoms and the like, and specifically, a hydrogen and methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, p-nitrobenzyl and the like. Preferred is methyl.

[0103]

As the acyloxylation agent in the step (4), for example, a quaternary ammonium carboxylate of the following formula (XI):

[0104]

[Chemical 56]



(XI)

[0105]

can be used. R^{11}, R^{12}, R^{13} and R^{14} independently represents an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms, and the like. Specifically, each includes methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, p-nitrobenzyl, and the like. Preferred is n-butyl.

[0106]

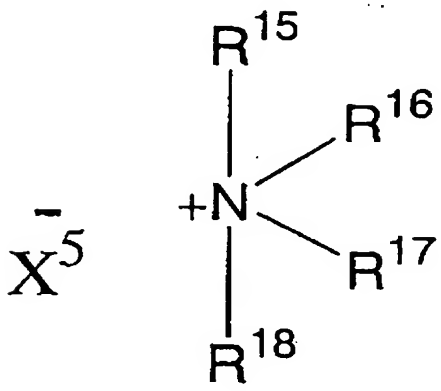
The amount of use of the quaternary ammonium carboxylate to be used here is 1 to 5 molar equivalents, preferably 1 to 3 molar equivalents relative to the halomethyldioxanyl acetic acid derivative.

[0107]

As the acyloxylation agent in the step (4), other than the quaternary ammonium carboxylate, a mixture of a quaternary ammonium salt of the following formula (XII):

[0108]

[Chemical 57]



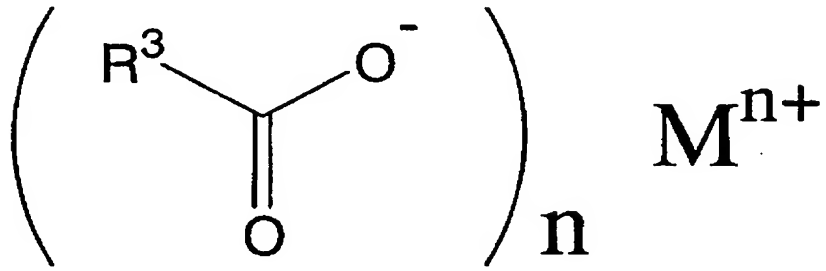
(XII)

[0109]

and a carboxylate of the following formula (XIII):

[0110]

[Chemical 58]



(XIII)

[0111]

can also be used.

[0112]

The above-mentioned acyloxylation reaction by the mixture of the quaternary ammonium salt and the carboxylate is the method which do not use an expensive ammonium carboxylate as well as use a small amount of the relatively expensive quaternary ammonium salt, and it is found by the present inventors for the first time.

[0113]

Referring to the above quaternary ammonium salt, R^{15}, R^{16}, R^{17} and R^{18} independently represents an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and the like, and specifically, methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, p-nitrobenzyl and the like. Preferred is n-butyl.

[0114]

Further, X^5 is a halogen atom, a hydroxy or acyloxy group and specifically, chlorine, bromine or iodine and hydroxy, acetoxy, butyroxy, benzyloxy, trifluoroacetoxy and the like. Preferred are chlorine, bromine, hydroxy and acetoxy. Still more preferred are chlorine or bromine.

[0115]

The amount of use of the above quaternary ammonium is 0.05 to 2 molar equivalent, preferably not more than the stoichiometric amount as a catalyst, specifically 0.1 to 0.9 molar equivalent relative to the halomethyldioxanyl acetic acid derivative.

[0116]

Referring to the above carboxylate, R^3 is a hydrogen, an alkyl group of 1 to 12 carbon atoms, an aryl group of 6 to 12 carbon atoms and an aralkyl group of 7 to 12 carbon atoms and the like, and specifically, hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-octyl, phenyl, naphthyl, p-methoxyphenyl, p-nitrobenzyl and the like. Preferred is methyl.

[0117]

M is an alkali metal or an alkaline earth metal and includes, specifically, lithium sodium, potassium, magnesium, calcium, barium, and the like. Preferred are sodium and potassium.

n depends on the valence of M and represents an integer of 1 or 2.

[0118]

The amount of use of the above carboxylate is 1 to 15 molar equivalents, preferably 1 to 5 molar equivalents relative to the halomethyldioxanyl acetic acid derivative.

[0119]

Further, preferred combination between X^5 of the quaternary ammonium salt and M of the carboxylate is the case when X^5 of the quaternary ammonium salt is chlorine and M of the carboxylate is sodium and the case when X^5 of the quaternary ammonium salt is bromine and M of the carboxylate is potassium.

[0120]

In the reaction of the step (4), various organic solvents may be used as a reaction solvent. As the above organic solvents, there may be mentioned, for example, hydrocarbon solvents such as benzene, toluene, cyclohexane, etc.; ether solvents such as diethyl ether, tetrahydrofuran, 1,4-dioxane, methyl t-butyl ether, dimethoxyethane, etc.; ester solvents such as ethyl acetate, butyl acetate, etc.; halogen containing solvents such as methylene chloride, chloroform, 1,1,1-trichloroethane, etc.; nitrogen-containing solvents such as N,N-dimethylformamide, acetamide, formamide, acetonitrile, etc.; aprotic polar solvents such as dimethyl sulfoxide, N-methylpyrrolidone, hexamethylphosphoric triamide and so on. The above solvents may be used each alone or in two or more of them may be used in a suitable combination. Preferred are nitrogen-containing solvents such as N,N-dimethylformamide, acetamide, formamide, acetonitrile, etc.; and aprotic polar solvents such as dimethyl sulfoxide, N-methylpyrrolidone, hexamethylphosphoric triamide, etc. More preferred is

N,N-dimethylformamide.

[0121]

The reaction temperature of the step (4) is 0℃ to 200℃, preferably 50℃ to 120℃.

[0122]

After completing the reaction of step (4), the routine aftertreatment may be carried out to recover the reaction product from a reaction mixture. For example, adding water to the reaction mixture at completion of the reaction and an extraction is carried out with the common extractant such as ethyl acetate, diethyl ether, methylene chloride, toluene and hexane. From the obtained extract, the reaction solvent and extractant are distilled by heating under reduced pressure or the like procedures, whereby the objective product can be obtained. Further, after completion of the reaction, the reaction solvent may be distilled immediately by heating under reduced pressure or the like procedures, followed by the same procedure. The objective product thus obtained is almost pure, however, it can be purified by the routine technique, such as crystallization, fractional distillation, column chromatography and/or the like to further enhance its purity.

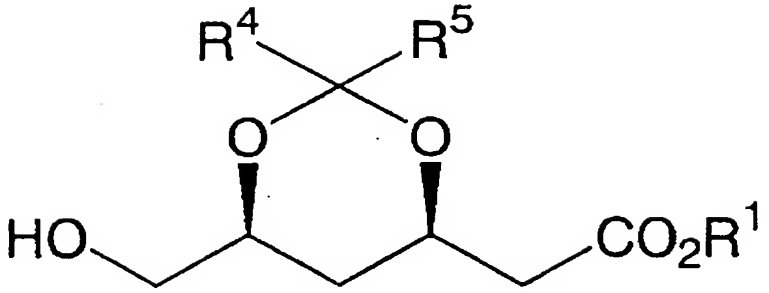
[0123]

Step (5)

In this step, a hydroxymethyldioxanyl acetic acid derivative having the (4R, 6S) configuration of the following formula (I):

[0124]

[Chemical 59]



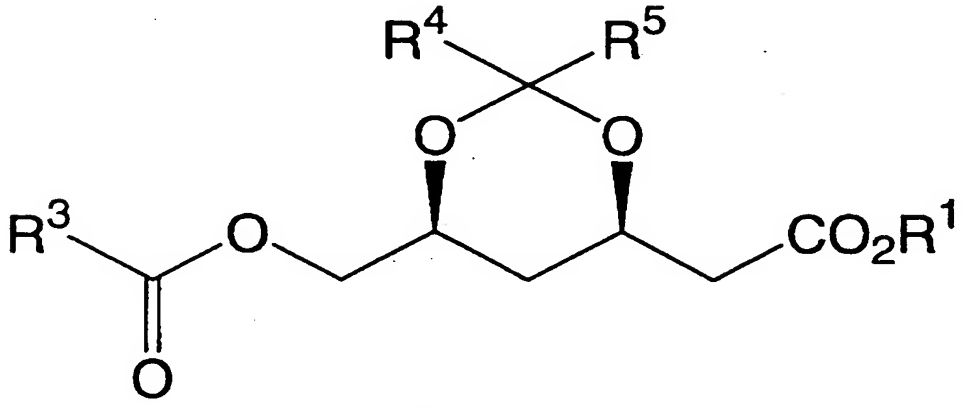
(I)

[0125]

is produced by subjecting the acyloxymethyldioxanyl acetic acid derivative having the (4R, 6S) configuration of the following formula (VII) obtained in the step (4):

[0126]

[Chemical 60]



(VII)

[0127]

to the solvolysis in the presence of a base using the known method or the like.

[0128]

Usable as the base for solvolysis in the step (5), there may be mentioned inorganic or organic bases, for example, sodium

carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide, barium hydroxide, magnesium hydroxide, sodium acetate, potassium acetate, ammonia, triethylamine, pyridine, piperidine, N,N-diaminopyridine and the like. Preferred is potassium carbonate.

[0129]

The amount of use of the base in this case is 0.001 to 5 equivalents, preferably 0.01 to 1.0 equivalents relative to the acyloxymethyldioxanyl acetic acid derivative.

[0130]

In the step (5), to conduct the solvolysis, the reaction is carried out in water, in a protic organic solvent, or in the mixed solvent of water or a protic organic solvent with an aprotic organic solvent. The above protic organic solvent includes, for example, alcohol solvents such as methanol, ethanol, butanol, isopropyl alcohol, ethylene glycol, methoxyethanol, etc.; and amine solvents such as diethylamine, pyrrolidine, piperidine, etc. The above aprotic organic solvent includes, for example, hydrocarbon solvents such as benzene, toluene, cyclohexane, etc.; ether solvents such as diethyl ether, tetrahydrofuran, 1,4-dioxane, methyl t-butyl ether, dimethoxyethane, etc.; ester solvents such as ethyl acetate, butyl acetate, etc.; ketone solvents such as acetone, methyl ethyl ketone, etc.; halogen containing solvents such as methylene chloride, chloroform, 1,1,1-trichloroethane, etc.; nitrogen-containing solvents such as dimethylformamide, acetonitrile, etc.; aprotic polar solvents such as dimethyl sulfoxide, N-methylpyrrolidone, hexamethylphosphoric triamide, etc.

Preferred are water, methanol and ethanol.

[0131]

The reaction temperature in the step (5) is -20℃ to 100℃, preferably -10℃ to 50℃.

[0132]

After completing the reaction of step (5), the routine aftertreatment may be carried out to recover the reaction product from a reaction mixture. For example, adding water to the reaction mixture at completion of the reaction and an extraction is carried out with the common extractant such as ethyl acetate, diethyl ether, methylene chloride, toluene and hexane. From the obtained extract, the reaction solvent and extractant are distilled by heating under reduced pressure or the like procedures, whereby the objective product can be obtained. Further, after completion of the reaction, the reaction solvent may be distilled immediately by heating under reduced pressure or the like procedures, followed by the same procedure. The objective product thus obtained is almost pure, however, it can be purified by the routine technique, such as crystallization, fractional distillation, column chromatography and/or the like to further enhance its purity.

[0133]

[Examples]

The present invention is described in further detail by the following examples, however, they are by no means limitative of the scope of the present invention. In the following description, "%" means "% by weight" without any specification.

[0134]

Example 1 Tert-butyl (5S)-6-chloro-5-hydoxy-3-oxohexanoate

Under argon gas, 3.34 g (33 mmol) of diisopropylamine was added dropwise to 16.7 g (30 mmol) of n-butyl magnesium chloride solution (1.8 mol/kg) in toluene/tetrahydrofuran (weight ratio; 1:2.5) mixture with stirring at 40℃ to prepare a magnesium diisopropylamide chloride solution.

[0135]

In 5.0 ml of dimethoxyethane were dissolved 1.0 g (6.0 mmol) of ethyl (3S)-4-chloro-3-hydroxybutyric acid (Patent 1723728) and 1.74 g (15 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 ℃. To this solution, the magnesium diisopropylamide chloride solution

prepared above was added dropwise over 3 hours, and the mixture was further stirred at 20 ℃ for 16 hours.

[0136]

In a separate vessel, 7.88 g of concentrated hydrochloric acid, 20 g of water and 20 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under reduced pressure.

[0137]

The residue was purified by silica gel column chromatography (Merck's Kieselgel 160, hexane:ethyl acetate = 80:20) to give 1.14 g of tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate (colorless oil) in 80% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz/ppm): 1.48 (9H, s), 2.84 (1H, dd), 2.91 (1H, dd), 3.05 (1H, bs), 3.41 (2H, s), 3.55-3.64 (2H, m), 4.28-4.36 (1H, m)

[0138]

Example 2 Tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate

Under argon gas, 1.0 g (6.0 mmol) of ethyl (3S)-4-chloro-3-hydroxybutyric acid and 2.78 g (24 mmol) of tert-butyl acetate were dissolved to 5.0 mL of tetrahydrofuran with stirring at 0 to 5 ℃. To this solution, tetrahydrofuran solution containing 24 mmol of lithium diisopropylamide was added dropwise over 20 minutes and the mixture was further stirred at 5 to 20 ℃ for 16 hours.

[0139]

In a separate vessel, 6.31 g of concentrated hydrochloric acid, 20 g of water and 20 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was then distilled off under

reduced pressure.

[0140]

The residue was purified by silica gel column chromatography (Merck's Kieselgel 160, hexane:ethyl acetate = 80:20) to give 86 mg of tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate (colorless oil) in 6% yield.

[0141]

Example 3 Tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate

In 10.0 ml of tetrahydrofuran were dissolved 3.0 g (18.0 mmol) of ethyl (3S)-4-chloro-3-hydroxybutyric acid, 5.22 g (45 mmol) of tert-butyl acetate and 6.86 g (72 mmol) of magnesium chloride, and the mixture was stirred in an argon atmosphere at 0 to 5 ℃. To this solution, the tetrahydrofuran solution containing 90 mmol of lithium diisopropylamide was added dropwise over 1 hour, and the mixture was further stirred at 25 ℃ for 3 hours.

In a separate vessel, 21.7 g of concentrated hydrochloric acid, 30 g of water, and 30 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was washed with water twice and the solvent was distilled off under reduced pressure to give 5.62 g of red oil containing tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate.

This oil was analyzed by high-performance liquid chromatography (column: Nacalai Tesque, Cosmosil 5CN-R (4.6 mm × 250 mm), eluent: water/acetonitrile = 9/1, flow rate: 1.0 ml/min, detection: 210 nm, column temperature: 40 ℃). The reaction yield was 65%.

[0142]

Example 4 Tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate

Under argon gas, a solution composed of 26.71 g (264 mmol) of diisopropylamine and 18.8 g of tetrahydrofuran was added dropwise to 150 mL (240 mmol) of n-butyl lithium/hexane solution (1.6 mol/L) with stirring at 5 ℃ to prepare a lithium

diisopropylamide solution.

[0143]

In 20 mL of tetrahydrofuran were dissolved 12.5 g (75 mmol) of ethyl (3S)-4-chloro-3-hydroxybutyric acid and 17.4 g (150 mmol) of tert-butyl acetate, and the solution was stirred in an argon atmosphere at 0 to 5 ℃. To this solution was added 42.9 g (75 mmol) of a solution of tert-butylmagnesium chloride (1.8 mol/kg) in toluene/tetrahydrofuran (weight ratio; 1:2.5) dropwise over 30 minutes, and the mixture was further stirred at 5 ℃ for 30 minutes. Then, the lithium diisopropylamide solution prepared above was added dropwise over 3 hours and the mixture was further stirred at 5 ℃ for 16 hours.

[0144]

In a separate vessel, 60.38 g of concentrated hydrochloric acid, 31.3 g of water, and 50 mL of ethyl acetate were mixed together under stirring and the above reaction mixture was poured. After standing, the organic layer was separated, washed with water twice and the solvent was distilled off under reduced pressure to give 22.0 g of red oil containing tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate.

The yield was analyzed by the method described in Example 3 and was 78%.

[0145]

Example 5 Tert-butyl (3R, 5S)-6-chloro-3,5-dihydroxy-hexanoate

The microorganisms indicated in Table 1 were seeded respectively in 50 ml of the above-mentioned A medium as sterilized in a 500 ml-volume Sakaguchi flask and shake-cultured aerobically at 30℃ for 2 days. The cells were collected by centrifugation from the culture fluid and suspended to 25 ml of 50mM phosphate buffer (pH 6.5) containing 1% tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate (synthesized by the method described in Example 1) and 2% glucose in a 500ml-volume Sakaguchi flask and shake-reacted at 30℃ for 20 hours. After the reaction, the reaction solution was extracted twice by adding

the same volume of ethyl acetate. Ethyl acetate layer was analyzed by high-performance liquid chromatography (column: Nacalai Tesque, Cosmosil 5CN-R (4.6 mm × 250 mm), eluent: 1 mM phosphoric acid aqueous solution/acetonitrile = 5/1, flow rate: 0.7 ml/min, detection: 210 nm, column temperature: 30 ℃) to detect the yield and diastereomer ratio of produced tert-butyl (3R, 5S)-6-chloro-3,5-dihydroxyhexanoate. The result is indicated in Table 1.

[0146]

[Table 11]

Microorganism	Yield (%)	Diastereomer ratio (3R, 5S) : (3S, 5S)
Hormoascus platypodis IFO1471	39	100:0
Candida catenulata IFO0745	41	100:0
Candida diversa IFO1019	33	100:0
Canidia fructus IFO1581	27	100:0
Candida glaebosa IFO1353	64	100:0
Canidida guilliermondii IFO0454	9	100:0
Cryptococcus humicola IFO0760	20	100:0
Candida intermedia IFO0761	24	94:6
Canidida magnoliae IFO0705	71	100:0
Candida musae IFO1582	24	100:0
Candida pintolopesii var. pintolopesii IFO0729	29	100:0
Candida pinus IFO0741	54	100:0
Candida sake IFO0435	32	100:0
Candida sonorensis IFO10027	23	100:0
Candida tropicalis IFO1401	28	95:5
Cryptococcus laurentii IFO0609	14	100:0
Cryptococcus terreus IFO0727	37	100:0
Debaryomyces hansenii var. fabryi IFO0058	16	100:0
Geotrichum eriense ATCC22311	24	89:11
Kuraishia capsulata IFO0721	12	100:0
Kluyveromyces marxianus IFO0288	8	100:0
Pichia bovis IFO1886	61	95:5
Yamadazyma haplophila IFO0947	10	100:0
Pichia membranaefaciens IFO0458	27	95:5
Rhodotorula glutinis IFO1099	12	100:0
Saccharomyces cerevisiae IFO0718	16	89:11
Schizoblastsporion kobayasii IFO1644	26	100:0
Candida claussenii IFO0759	24	90:10
Debaryomyces robertsii IFO1277	20	100:0
Zygosaccharomyces rouxii IFO0493	22	89:11

[0147]

Example 6 Tert-butyl (3R, 5S)-6-chloro-3,5-dihydroxy-hexanoate

Candida magnoliae IFO0705 was seeded in a 5L-volume mini jar fermenter containing 3L of the A medium and cultured at 30℃, with aeration of 0.5vvm and agitation of 500rpm for 24 hours. After completion of the cultivation, 30 g of tert-butyl (5S)-6-chloro-5-hydroxy-3-oxohexanoate (synthesized by the method described in Example 1) and 60 g of glucose were added and the reaction was carried out for 18 hours while maintaining pH at 6.5 with sodium hydroxide. After the completion of the reaction, cells were removed by centrifugation and the resulting supernatant was extracted twice with 1.5L ethyl acetate. The organic layer thus obtained was dehydrated with anhydrous sodium sulfate, desolvated under reduced pressure to give 24 g solid of tert-butyl (3R, 5S)-6-chloro-3,5-dihydroxy- hexanoate. The diastereomer ratio of the same was analyzes by the method described in Example 5 and found as (3R, 5S)/ (3S, 5S) = 100/0. ^{1}H-NMR ($CDCl_3$, 400 MHz/ppm): 1.47 (9H, s), 1.62-1.78 (2H, m), 2.43 (2H, d, J=6.4 Hz), 3.51-3.58 (2H, m), 3.75 (1H, bs), 3.84 (1H, bs), 4.07-4.13 (1H, m), 4.23-4.28 (1H, m)

[0148]

Example 7 Tert-butyl 2-[(4R, 6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid

In 4.0 ml of acetone was dissolved 1.08g (4.52 mmol) of tert-butyl (3R, 5S)-6-chloro-3,5-dihydroxyhexanoate (synthesized by the method described in Example 6) and 0.83 ml (6.8 mmol) of 2,2-dimethoxypropane and 8.6 mg (0.045 mmol) of p-toluenesulfonic acid were added followed by stirring for 4.5 hours at room temperature. The reaction solvent and excess 2,2-dimethoxypropane were distilled off under reduced pressure. The residue was added with 10 ml of saturated aqueous sodium bicarbonate solution and extracted three times with n-hexane.

The extracted organic layer was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium

sulfate and the solvent was distilled off under reduced pressure to give 1.25g of tert-butyl 2-[(4R, 6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl] acetic acid (colorless oil) in 99% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz/ppm): 1.25 (1H, dd), 1.39 (3H, s), 1.45 (9H, s), 1.47 (3H, s), 1.77 (1H, dt), 2.33 (1H, dd), 2.46 (1H, dd), 2.40 (1H, dd), 2.51 (1H, dd), 4.03-4.10 (1H, m), 4.25-4.30 (1H, m)

[0149]

Example 8 Tert-butyl 2-{(4R, 6S)-2,2-dimethyl-6-[(methylcarbonyloxy)methyl]-1,3-dioxane-4-yl} acetic acid

In 10 ml of N,N-dimethylformamide were suspended 1.00 g (3.60 mmol) of tert-butyl 2-[(4R, 6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl] acetic acid (synthesized by the method described in Example 7), 1.16 g (3.60 mmol) of tetra n-butyl ammonium bromide and 1.76 g (18.0 mmol) of potassium acetate and stirred at 100℃ for 20 hours. After cooling down to room temperature, 20 ml of water was added and extracted three times with n-hexane.

The extracted organic layer was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (Merck's Kieselgel 160, hexane:ethyl acetate = 80:20) to give 0.88 g of tert-butyl 2-{(4R, 6S)-2,2-dimethyl-6-[(methylcarbonyloxy)methyl]-1,3-dioxane-4-yl} acetic acid (white solid) in 81% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz/ppm): 1.27 (1H, dd, J=23.9, 11.7 Hz), 1.39 (3H, s), 1.45 (9H, s), 1.47 (3H, s), 1.57 (1H, dm, J=10.3 Hz), 2.08 (3H, s), 2.32 (1H, dd, J=15.1, 5.9 Hz), 2.45 (1H, dd, J=15.1, 6.8 Hz), 3.97-4.16 (3H, m), 4.25-4.33 (1H, m)

[0150]

Example 9 Tert-butyl 2-{(4R, 6S)-2,2-dimethyl-6-[(methylcarbonyloxy)methyl]-1,3-dioxane-4-yl} acetic acid

In 10 ml of N,N-dimethylformamide were suspended 1.00 g

(3.60 mmol) of tert-butyl 2-[(4R, 6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl] acetic acid, 0.5 g (1.80 mmol) of tetra n-butyl ammonium chloride and 0.89 g (10.8 mmol) of sodium acetate and stirred at 100℃ for 20 hours. After cooling down to room temperature, 20 ml of water was added and extracted three times with n-hexane.

The extracted organic layer was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was added with 8.0 ml of n-hexane again, dissolved by heating to 50℃ and cooled to -20℃. The crystallized material was separated by filteration, washed with cold n-hexane, dried under reduced pressure to give 0.76 g of tert-butyl 2-{(4R, 6S)-2,2-dimethyl-6-[(methylcarbonyloxy)methyl]-1,3-dioxane-4-yl} acetic acid (white needle crystal) in 70% yield.

[0151]

Example 10 Tert-butyl 2-[(4R, 6S)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-yl] acetic acid

In 100 ml of methanol was dissolved 10 g (33.1 mmol) of tert-butyl 2-{(4R, 6S)-2,2-dimethyl-6-[(methylcarbonyloxy)-methyl]-1,3-dioxane-4-yl} acetic acid and 0.46 g (3.3 mmol) of potassium carbonate was added under ice-cooled stirring. The ice-cooled stirring was kept for 4 hours. The solvent was distilled off from the reaction mixture under reduced pressure, 50 ml of water was added and neutralized with 0.1N hydrochloric acid. The above solution was extracted with ethyl acetate and thus obtained organic layer was washed with water, dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The oil obtained as the residue was kept under high vacuum of not more than 1 Torr with using a vacuum pump to remove the solvent almost completely to give 8.6 g of tert-butyl 2-[(4R, 6S)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane- 4-yl] acetic acid (colorless oil) in 100% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz/ppm): 1.29-1.52 (2H, m), 1.39 (3H, s), 1.45 (9H, s), 1.47 (3H, s), 2.05 (1H, bs), 2.33 (1H, dd, J=15.1,

5.9 Hz), 2.44 (1H, dd, J=15.1, 6.8 Hz), 3.47-3.53 (1H, m), 3.58-3.64 (1H, m), 3.99-4.04 (1H, m), 4.27-4.33 (1H, m)

[0152]

[Effect of the Invention]

The present invention, constituted as described above, enables the production of optically active 2-[6-(hydroxymethyl)-1,3-dioxane-4-yl] acetic acid derivatives, which are of use as pharmaceutical intermediates, particularly intermediates of HMG-CoA reductase inhibitors, from inexpensive, readily available starting compounds without using any extraordinary production equipment such as a very-low-temperature reactor.

[Document Name] Abstract

[Abstract]

[Subject] The object of the present invention is to provide a production process by which an optically active 2-[6-(hydroxymethyl)-1,3-dioxane-4-yl] acetic acid derivative, a useful pharmaceutical intermediate, can be prepared easily from an inexpensive starting material without using any extraordinary production equipment such as a very-low-temperature reactor.

[Means for Solving] Thus, this invention provides a process for producing an optically active 2-[6-(hydroxymethyl)-1,3-dioxane-4-yl] acetic acid derivative which comprises reacting an enolate prepared by permitting any of a base and a nonvalent metal to act upon an acetic acid ester derivative with a hydroxybutyric acid derivative at not below -30 ℃ to produce a hydroxyoxohexanoate derivative,

reducing this compound with using a microorganism to produce a dihydroxyhexanoate derivative,

treating this compound with an acetal forming reaction agent in the presence of an acid catalyst to produce halomethyldioxanyl acetic acid derivative,

further subjecting this compound for acyloxylation with an acyloxylating agent to produce an acyloxymethyldioxanyl acetate derivative,

and finally, subjecting it for solvolysis in the presence of a base.

[Selective Figure] None